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Review Article

Pharmaceutical Perspectives on Semaglutide: Formulation Drug Delivery and Clinical Applications

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ABSTRACT

A glucagon-like peptide-1 receptor agonist (GLP-1 RA), semaglutide, has become a key treatment for obesity and type 2 diabetes mellitus (T2DM). Significant weight reduction is induced, glycaemic management is improved, and the risk of serious adverse cardiovascular events is decreased. Semaglutide comes in injectable (Ozempic®, Wegovy®) and oral (Rybelsus®) formulations. It has good pharmacokinetic qualities, such as a long half-life and high bioavailability, which permits once-weekly dosage. Its mode of action, absorption, distribution, metabolism, and excretion (ADME), clinical indications, therapeutic efficacy, side effects, and safety considerations are all reviewed in this article benefits, and we provide insights into future directions where artificial intelligence-driven drug carrier design, personalized nanomedicine, and combination therapies may play pivotal roles in next-generation cancer treatment. Collectively, these nanotechnologies represent a paradigm shift in oncology, moving toward precision, personalization, and reduced treatment burden.

INTRODUCTION

Semaglutide a glucagon like peptide 1 receptor agonist has shown to reduce the risk of adverse cardiovascular events in patients with diabetics. Whether semaglutide can reduce cardio vascular risk associated with overweight and obesity in the absence of diabetics in unknown. The glucagon like peptide – 1 receptor agonist (GLP – 1 RA) Semaglutide is the mostly recently approved agent of drug class, and GLP – 1RA Currently available as both subcutaneous and oral formulation and oral formulation. While GLP -1RA effectively improve glycaemic control and cause weight loss, potential safety concerns arisen over the years. The expanded scope for these therapies warrants comprehensive safety evaluations. We report the safety of subcutaneous and oral semaglutide from the SUSTAIN and PIONEER clinical trial

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programmes respectively [1,2]. Semaglutide received approval in 2021 for chronic weight management [3].

Example: Ozempic @, Rybelsus @, and Wegovy @.

- Ozempic - Injection
- Rybelsus - Tablet
- Wegovy- Injection

Mechanism Of Action:

Although semaglutide's exact mode of action is unknown, it is well-characterized. As an agonist of the glucagon-like peptide-1 (GLP-1) receptor, semaglutide binds to GLP-1 receptors in the brain, pancreas, and gastrointestinal tract to improve the regulation of incretin activities [3,4]. Semaglutide promotes the pancreatic β-cells' glucose-dependent insulin production in response to high blood glucose levels in order to preserve glucose homeostasis [5,6]. Semaglutide lowers blood sugar levels by decreasing glucagon release and increasing insulin secretion[7,5] . Type 2 diabetes can be effectively treated with this dual action, which lowers hyperglycaemia without increasing the risk of hypoglycaemia.

Formulations:

Injectable solutions: Ozempic® (subcutaneous weekly), Wegovy® (subcutaneous weekly, higher dose for obesity).

Oral tablets: Rybelsus® (first oral GLP-1 RA, co-formulated with absorption enhancer sodium N-(8-[2-hydroxybenzoyl]amino) caprylate, SNAC to increase gastric uptake).

2. Stability & Storage

Injectable semaglutide must be stored refrigerated (2–8 °C), protected from light. Oral tablets are sensitive to humidity and should be stored in original blister packs. Stable peptide structure due to albumin binding and fatty-acid chain modification.

Drug Delivery Challenges:

Being a peptide drug, oral delivery is difficult due to enzymatic degradation and poor permeability. SNAC in Rybelsus® enhances transcellular absorption by protecting semaglutide from proteolysis and increasing local pH in the stomach.

4. Excipients Used

Oral formulation contains magnesium stearate, microcrystalline cellulose, and SNAC as absorption enhancer. Injectable pens contain disodium phosphate, propylene glycol, and phenol as stabilizers.

ADME Process of Semaglutide:

Adsorption:

One dose of semaglutide 0.5 mg administered subcutaneously to healthy people results in a maximum concentration (Cmax) in 24–56 hours (REFS 8,9). Weekly semaglutide 0.25 mg doses for four weeks, followed by 0.5 mg for four weeks, and then 1.0 mg for five weeks, were used in dose-escalation trials. These investigations revealed a period similar to Cmax of 33–36 hours following the last 1.0 mg dosage (REFS 10,11). Following a final 1.0 mg dose during a dose escalation and after a single 0.5 mg dose, Cmax and the area under the plasma concentration–time curve (AUC) is comparable (REFS 8,9,10,11). Semaglutide has the highest subcutaneous bioavailability of any GLP-1 RA presently on the market, at 94% (REFS 12,13,14,15).

Distribution:

For once-weekly dosing, semaglutide was designed to be an equivalent of liraglutide with a higher binding affinity for albumin. Lau et al. demonstrated in living pigs that semaglutide had a half-life of roughly 46 hours after intravenous treatment, while liraglutide had a half-life of 12 hours (REF 12). Greater binding to albumin was indicated by semaglutide's slower clearance (0.0016 vs. 0.0038 L/h/kg) and larger volume of distribution (0.102 L/kg versus 0.067 L/kg).

Metabolism:

A single subcutaneous dosage of radiolabelled [3H]-semaglutide was administered to seven healthy males as part of an absorption, metabolism, and excretion study to examine semaglutide metabolism (REF 8). According to metabolite profiling, semaglutide is broken down into six distinct metabolites, designated P1–P3 and P5–P7. [3H]-semaglutide, the Parent molecule P4, was the main component found in plasma (82.6%). Beta-oxidation of the fatty acid side chain and proteolytic cleavage of the peptide backbone are the processes by which semaglutide is metabolized. Over time, the metabolite concentrations decreased until, 28 days after dosage, only the parent substance was found in plasma. The metabolites' potential contribution to semaglutide's side effects or effectiveness is unknown.

Excretion:

This study also reported on the excretion of radiolabelled [3H]-semaglutide and its metabolites (REF 8). After 0.5 mg semaglutide was administered subcutaneously once, 75% of the dosage was recovered after 64 days of collection. Urine contained 53%, faces 18.6%, and expired air contained 3.2%. 21 metabolites and the parent semaglutide molecule were found in urine. It was discovered that approximately 3% of the dose was [3H]-semaglutide, with two metabolites (P6 and P7) making up 14% of the dose and the remaining metabolites making up less than 2%. There would be no need to modify dosage based on renal status because there was very little intact medication in the urine. The faces did not contain any parent drugs.

Wegovy:

Indications And Usage:

- WEGOVY® is indicated in combination with a reduced calorie diet and increased physical activity:
- to reduce the risk of major adverse cardiovascular events (Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.
- to reduce excess body weight and maintain weight reduction long term in:
- Adults and paediatric patients aged 12 years and older with obesity
- Adults with overweight in the presence of at least one weight-related comorbid condition.

Usage:

- Patients with type 2 diabetes mellitus, monitor blood glucose prior to starting WEGOVY® and during WEGOVY® treatment [see Warnings and Precautions (5.4)].
- Prior to initiation of WEGOVY®, train patients on proper
- injection technique. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.
- Inspect WEGOVY® visually prior to each injection. Only use if solution is clear, colourless, and contains no particles.

- Administer WEGOVY® in combination with a reduced-calorie diet and increased physical activity.
- Administer WEGOVY® once weekly, on the same day each week, at any time of day, with or without meals.
- Inject WEGOVY® subcutaneously in the abdomen, thigh, or upper arm. The time of day and the injection site can be changed without dose adjustment.

Adverse Reactions

- Thyroid C-cell tumors (contraindicated in patients with MTC or MEN2)
- Pancreatitis
- Gallbladder disease
- Diabetic retinopathy complications in T2DM patients
- Hypoglycaemia when used with insulin or sulfonylureas
- Risk of Thyroid C-Cell Tumours
- Acute Pancreatitis
- Acute Gallbladder Disease
- Hypoglycaemia
- Acute Kidney Injury
- Severe Gastrointestinal Adverse Reactions
- Hypersensitivity Reactions
- Diabetic Retinopathy Complications in Patients with Type 2
- Diabetes

Clinical Trials Experience:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Drug Interactions

7.1 Concomitant Use with Insulin or an Insulin Secretagogue (e.g., Sulfonylurea)

WEGOVY® lowers blood glucose and can cause hypoglycaemia. The risk of hypoglycaemia is increased when WEGOVY® is used in combination with insulin or insulin secretagogues (e.g., sulfonylureas). The addition of WEGOVY® in patients treated with insulin has not been evaluated. When initiating WEGOVY®, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of Hypoglycaemia. Oral Medications WEGOVY ® causes a delay of gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials with semaglutide 1 mg, semaglutide did not affect the absorption of orally administered medication , monitor the effects of oral medications concomitantly administered with WEGOVY®.

Ozempic:

Ozempic® is an injectable prescription medicine used:

- along with diet and exercise to improve blood sugar (glucose) in adults with type 2 diabetes mellitus.
- to reduce the risk of major cardiovascular events such as heart attack, stroke or death in adults with type 2 diabetes mellitus with known heart disease.
- to reduce the risk of kidney disease worsening, kidney failure (end-stage kidney disease), and death due to cardiovascular disease in adults with type 2 diabetes mellitus and chronic kidney disease.
- It is not known if OZEMPIC® is safe and effective for use in children.

Not Use for Ozempic Injection:

you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2.

Indications And Usage:

Ozempic® is indicated:

as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. to reduce the risk of sustained eGFR decline, end-stage kidney disease, and cardiovascular death in adults with type 2 diabetes mellitus and chronic kidney disease.

Dosage And Administration:

- Inspect OZEMPIC® visually before use. It should appear clear and colourless. Do not use OZEMPIC ® if particulate matter and coloration is seen.
- Administer OZEMPIC® once weekly, on the same day each week, at any time of the day, with or without meals.
- Inject OZEMPIC® subcutaneously in the abdomen, thigh, or upper arm. Instruct patients to use a different injection site each week when injecting in the same body region.
- When using OZEMPIC® with insulin, instruct patients to administer as separate injections and to never mix the products. It is acceptable to inject OZEMPIC® and insulin in the same body region, but the injections should not be adjacent to each other.
- The day of weekly administration can be changed, if necessary, as long as the time between two doses is at least 2 days (>48 hours).
- If a dose is missed, administer OZEMPIC® as soon as possible within 5 days after the missed dose. If more than 5 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

Drug Interactions:

Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with

Insulin:

OZEMPIC® stimulates insulin release in the presence of elevated blood glucose concentrations. Patients receiving OZEMPIC ® in combination with an insulin secretagogue (e.g., sulfonylurea) or Insulin may have an increased risk of hypoglycaemia, including severe hypoglycaemia. When initiating OZEMPIC®, consider reducing the dose of concomitantly administered insulin secretagogue.

Adverse Reactions:

Oral Medications:

OZEMPIC® causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, semaglutide did not affect the absorption of orally administered medications to any clinically relevant degree .Nonetheless, caution should be exercised when oral medications are concomitantly administered with OZEMPIC®.

CONCLUSION:

Semaglutide offers better glycaemic control, cardiovascular protection, and long-lasting weight loss, making it a breakthrough in the treatment of type 2 diabetes and obesity. Patient compliance is increased by its dual availability as injectable and oral formulations. Pharmaceutically speaking, semaglutide is a model for peptide drug development due to its novel formulation techniques, which include fatty acid modification for prolonged half-life and oral delivery made possible by SNAC. It is still a mainstay of contemporary diabetes treatment, despite its expense and storage restrictions.

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